

# **SUPPLEMENTAL MATERIAL**

**Table S1. Characteristics of cases and controls. New-user approach.**

	<b>Cases (%) n= 2,493</b>	<b>Controls (%) n= 18,092</b>	<b>Non adjusted OR* (95% CI)</b>
Age mean in years ( $\pm$ SD)	71.81 (10.95)	71.76 (11.27)	1.00 (1.00-1.00)
Men	1,373 (55.07)	10,067 (55.64)	1.02 (0.94-1.12)
Visits (n)			
<6	282 (11.31)	3,358 (18.56)	1 (ref.)
6-15	848 (34.02)	7,399 (40.90)	1.42 (1.24-1.64)
16-24	724 (29.04)	4,359 (24.09)	2.10 (1.81-2.44)
25 +	639 (25.63)	2,976 (16.45)	2.73 (2.34-3.19)
History of IHD (no AMI)	158 (6.34)	917 (5.07)	1.30 (1.09-1.55)
History of TIA	85 (3.41)	260 (1.99)	1.74 (1.37-2.22)
History of AMI	175 (7.02)	971 (5.37)	1.34 (1.13-1.58)
Heart failure	137 (5.50)	626 (3.46)	1.63 (1.34-1.97)
History of Atrial fibrillation	238 (9.55)	906 (5.01)	2.02 (1.74-2.35)
Hypertension	1,476 (59.21)	9,011 (49.81)	1.49 (1.37-1.63)
Dyslipidemia	913 (36.62)	6,014 (33.24)	1.15 (1.06-1.26)
Diabetes	867 (34.78)	3,809 (21.05)	2.01 (1.83-2.20)
PAD	103 (4.13)	456 (2.52)	1.68 (1.35-2.09)
COPD	247 (9.91)	1,601 (8.85)	1.15 (0.99-1.33)
Depression	348 (13.96)	1,790 (9.89)	1.48 (1.30-1.67)
Hyperuricaemia	117 (4.69)	722 (3.99)	1.21 (0.99-1.48)
Gout	125 (5.01)	668 (3.69)	1.41 (1.15-1.71)
Renal failure	112 (4.49)	534 (2.95)	1.54 (1.25-1.90)
Rheumatoid arthritis	14 (0.56)	144 (0.80)	0.70 (0.40-1.21)
Osteoarthritis	721 (28.92)	4,746 (26.23)	1.14 (1.04-1.26)
Smoking			
Never smoker	839 (33.65)	6,236 (34.47)	1 (ref.)
Current smoker	694 (27.84)	4,412 (24.39)	1.17 (1.05-1.31)
Past smoker	247 (9.91)	1,522 (8.41)	1.20 (1.03-1.40)
No record	713 (28.60)	5,922 (32.73)	0.90 (0.81-1.00)
Alcohol abuse	522 (20.94)	3,002 (16.59)	1.38 (1.24-1.54)
BMI (kg/m <sup>2</sup> )			
<25	306 (12.27)	2,008 (11.10)	1 (ref.)
25-30	771 (30.93)	5,269 (29.12)	0.96 (0.83-1.11)
>30	698 (28.00)	4,341 (23.99)	1.05 (0.91-1.22)
No record	718 (28.80)	6,474 (35.78)	0.73 (0.63-0.84)

**Table S1 (continued). Characteristics of cases and controls. New-user approach.**

	<b>Cases (%) n= 2,493</b>	<b>Controls (%) n= 18,092</b>	<b>Non adjusted OR* (95% CI)</b>
Drug use (current) of:			
Low-dose aspirin	470 (18.85)	2,196 (12.14)	1.77 (1.58-1.98)
Non-aspirin antiplatelet	147 (5.90)	659 (3.64)	1.68 (1.40-2.02)
Alpha blockers	81 (3.25)	527 (2.91)	1.14 (0.90-1.45)
Calcium-channel blockers	384 (15.40)	2,209 (12.21)	1.41 (1.25-1.59)
Beta-blockers	269 (10.79)	1,409 (7.79)	1.46 (1.27-1.68)
ACE inhibitors	568 (22.78)	3,279 (18.12)	1.46 (1.31-1.62)
AT II receptor blockers	301 (12.07)	1,786 (9.87)	1.28 (1.12-1.46)
Nitrates	164 (6.58)	838 (4.63)	1.49 (1.25-1.77)
Oral anticoagulants	133 (5.33)	767 (4.24)	1.28 (1.06-1.55)
Diuretics-high ceiling	291 (11.67)	1,310 (7.24)	1.79 (1.56-2.05)
Diuretics-low ceiling	231 (9.27)	1,824 (10.08)	0.93 (0.80-1.08)
Diuretics K sparing	47 (1.89)	217 (1.20)	1.59 (1.15-2.18)
Corticosteroids	40 (1.60)	315 (1.74)	0.93 (0.67-1.30)
NSAIDs	295 (11.83)	2,017 (11.15)	1.09 (0.95-1.25)
Paracetamol	415 (16.65)	2,950 (16.31)	1.09 (0.96-1.24)
Metamizole	92 (3.69)	646 (3.57)	1.07 (0.86-1.34)
Colchicine	16 (0.64)	67 (0.37)	1.77 (1.02-3.06)
Allopurinol	93 (3.73)	559 (3.09)	1.22 (0.97-1.53)
PPI	537 (21.54)	3,354 (18.54)	1.21 (1.09-1.36)
H2 blockers	76 (3.05)	562 (3.11)	1.00 (0.78-1.27)

\* Adjusted only for matching factors (age, sex and calendar year).

AMI: Acute myocardial infarction; IHD: Ischemic heart disease; TIA: Transient ischemic attack; PAD: Peripheral artery disease; COPD: Chronic obstructive pulmonary disease; BMI: Body mass index; ACE: Angiotensin converting enzyme; ATII: Angiotensin II; NSAIDs: Non-steroidal anti-inflammatory drugs; PPI: Proton pump inhibitors; H2: Histamine receptor type 2.

**Table S2. Risk of ischemic stroke associated with the use of fixed-dose combination of calcium and vitamin D supplements (CaD) and the effect of dose and duration of treatment. New-user approach.**

	<b>Cases (%) n= 2,493</b>	<b>Controls (%) n= 18,092</b>	<b>Non adjusted OR<sup>†</sup> (95% CI)</b>	<b>Adjusted OR<sup>‡</sup> (95% CI)</b>
<i>CaD</i>				
Non use	2,407 (96.55)	17,432 (96.35)	1 (ref.)	1 (ref.)
Current	27 (1.08)	279 (1.54)	0.68 (0.46-1.02)	0.67 (0.44-1.00)
Recent	39 (1.56)	221 (1.22)	1.25 (0.89-1.77)	1.19 (0.83-1.70)
Past	20 (0.80)	160 (0.88)	0.87 (0.55-1.39)	0.82 (0.51-1.33)
<i>Calcium dose*</i>				
<1000mg	11 (0.44)	121 (0.67)	0.64 (0.34-1.19)	0.64 (0.34-1.20)
≥1000mg	8 (0.32)	93 (0.51)	0.61 (0.29-1.25)	0.55 (0.26-1.16)
Unknown	8 (0.32)	65 (0.36)	0.87 (0.41-1.81)	0.91 (0.43-1.93)
<i>Duration*</i>				
≤180 days	18 (0.72)	174 (0.96)	0.73 (0.45-1.19)	0.75 (0.46-1.24)
>180 days	9 (0.36)	105 (0.58)	0.60 (0.30-1.19)	0.54 (0.27-1.09)

\* Among current users.

<sup>†</sup> Adjusted only for matching factors (age, sex and calendar year).

<sup>‡</sup> Adjusted for matching factors and for all factors included in Table 1.

**Table S3. Risk of ischemic stroke associated with the use of calcium in monotherapy (CaM) and the effect of dose and duration of treatment. New-user approach.**

	<b>Cases (%) n= 2,493</b>	<b>Controls (%) n= 18,092</b>	<b>Non adjusted OR<sup>†</sup> (95% CI)</b>	<b>Adjusted OR<sup>‡</sup> (95% CI)</b>
<i>CaM</i>				
Non use	2,458 (98.60)	17,884 (98.85)	1 (ref.)	1 (ref.)
Current	16 (0.64)	78 (0.43)	1.48 (0.86-2.53)	1.20 (0.69-2.11)
Recent	12 (0.48)	69 (0.38)	1.24 (0.67-2.30)	1.26 (0.67-2.38)
Past	7 (0.28)	61 (0.34)	0.81 (0.37-1.77)	0.78 (0.35-1.74)
<i>Calcium dose*</i>				
<1000mg	6 (0.24)	38 (0.21)	1.05 (0.44-2.48)	0.84 (0.34-2.04)
≥1000mg	10 (0.40)	17 (0.09)	5.13 (2.27-11.56)	3.99 (1.71-9.34)
Unknown	-	23 (0.13)	-	-
<i>Duration*</i>				
≤180 days	7 (0.28)	49 (0.27)	1.03 (0.47-2.28)	0.82 (0.36-1.87)
>180 days	9 (0.36)	29 (0.16)	2.22 (1.05-4.70)	1.84 (0.85-3.98)

\* Among current users.

† Adjusted only for matching factors (age, sex and calendar year).

‡ Adjusted for matching factors and for all factors included in Table 1.

**Table S4. Evaluation of the potential interaction of fixed-dose combination of calcium and vitamin D supplements (CaD) with sex, age and baseline CV risk with respect to the risk of ischemic stroke.**

<b>Current use of CaD by</b>	<b>Cases (%) n= 2,493</b>	<b>Controls (%) n= 18,092</b>	<b>Non adjusted OR* (95% CI)</b>	<b>Adjusted OR† (95% CI)</b>
<i>Sex</i>				
Male	3 (0.22)	43 (0.43)	0.51 (0.16-1.65)	0.55 (0.17-1.82)
Female	24 (2.14)	236 (2.94)	0.72 (0.47-1.10)	0.69 (0.44-1.07)
				Test for interaction, p=0.726
<i>Age</i>				
< 70	6 (0.69)	57 (0.89)	0.75 (0.32-1.76)	0.67 (0.27-1.68)
70 +	21 (1.29)	222 (1.90)	0.66 (0.42-1.04)	0.66 (0.41-1.05)
				Test for interaction, p=0.977
<i>CV risk</i>				
Low-intermed.	19 (1.42)	213 (1.66)	0.83 (0.52-1.33)	0.79 (0.49-1.29)
High	8 (0.69)	66 (1.25)	0.53 (0.25-1.11)	0.49 (0.22-1.02)
				Test for interaction, p=0.302

\* Adjusted only for matching factors (age, sex and calendar year).

† Adjusted for matching factors and for all factors included in Table 1.

**Table S5. Evaluation of the potential interaction of calcium in monotherapy (CaM) with sex, age and baseline CV risk with respect to the risk of ischemic stroke.**

<b>Current use of CaM by</b>	<b>Cases (%) n= 2,493</b>	<b>Controls (%) n= 18,092</b>	<b>Non adjusted OR* (95% CI)</b>	<b>Adjusted OR† (95% CI)</b>
<i>Sex</i>				
Male	5 (0.36)	15 (0.15)	2.43 (0.88-6.72)	1.91 (0.66-5.55)
Female	11 (0.98)	63 (0.79)	1.25 (0.66-2.38)	1.04 (0.53-2.05)
				Test for interaction, p=0.347
<i>Age</i>				
< 70	5 (0.57)	24 (0.38)	1.50 (0.57-3.97)	1.25 (0.43-3.60)
70 +	11 (0.68)	54 (0.46)	1.47 (0.76-2.81)	1.18 (0.60-2.32)
				Test for interaction, p=0.936
<i>CV risk</i>				
Low-intermed.	10 (0.75)	54 (0.42)	1.76 (0.89-3.46)	1.41 (0.70-2.84)
High	6 (0.52)	24 (0.46)	1.10 (0.45-2.70)	0.86 (0.34-2.20)
				Test for interaction, p=0.406

\* Adjusted only for matching factors (age, sex and calendar year).

† Adjusted for matching factors and for the variables described in methods and Table 1.

**Table S6. Number Needed to treat with high-dose calcium supplements to have one patient Harmed (NNH) per year under different scenarios**

		Incidence of ischemic stroke per 100,000 person-years in the population	Incidence of ischemic stroke among users of high-dose calcium supplements in monotherapy ( $\geq 1000\text{mg Ca}$ ) per 100,000 person-years (assuming a RR=2)	Attributable Risk among exposed to high-dose calcium supplements in monotherapy ( $\geq 1000\text{mg Ca}$ ) per 100,000 person-years	NNH
USA <sup>*†</sup>	Men	372	744	372	269
	Women	288	576	288	347
	Overall	325	650	325	308
	< 65 years	191	382	191	524
	$\geq 65$ years	460	920	460	217
Spain <sup>‡</sup>	Men	128	256	128	781
	Women	106	212	106	943
	Overall	118	236	118	847

\*Koton S, Schneider AL, Rosamond WD, Shahar E, Sang Y, Gottesman RF, Coresh J. Stroke incidence and mortality trends in US communities, 1987 to 2011. *JAMA*. 2014;312:259-68.

† Assuming that 87% was ischemic stroke (Koton et al, 2014).

‡ Díaz-Guzman J, Egido JA, Gabriel-Sánchez R, Barberá-Comes G, Fuentes-Gimeno B, Fernández-Perez C. Stroke and transient ischemic attack incidence rate in Spain: the IBERICTUS study. *Cerebrovasc Dis*. 2012; 34: 272-281.